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Melanopsin-expressing retinal ganglion cells in aging and disease

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Abstract

Melanopsin-expressing retinal ganglion cells (mRGCs) constitute a system in the mammalian retina used for irradiance detection, regulating non-image forming functions, such as photoentrainment of circadian rhythms, control of the pupillary light reflex, masking response, light-regulated melatonin secretion, and modulation of the sleep/wake cycle. There are five subtypes of mRGCs differentiated by morphology and function. Recent years of research on mRGCs have identified a broad number of neurodegenerative diseases in the eye and the brain with altered physiologic light responses, leading to disturbances of non-image forming light response(s). In this review, we briefly summarise the melanopsin system in the normal retina and discuss its role in connection to human aging (sleep/wake problems) and retinal pathology in Alzheimer and Parkinson diseases, diabetic retinopathy, mitochondrial optic neuropathies, glaucoma, retinitis pigmentosa, and in photophobia during migraine and in seasonal affective disorder (SAD). Finally, we discuss the diagnostic tools that are being used to differentiate retinal diseases involving the melanopsin system in the rods and cones from the inner versus the outer retina.

1. Introduction

The mammalian eye contains a subset of retinal ganglion cells which are intrinsically photosensitive due to the expression of the photopigment melanopsin (OPN4). The melanopsin-expressing retinal ganglion cells (mRGCs), which show maximum sensitivity to the short-wavelength blue light, have been recently identified as a class of photoreceptors that mainly support non-image forming (NIF) visual functions of the eye (Do and Yau, 2010). These include photoentrainment of circadian rhythms, masking, sleep regulation, pupillary light reflex, and light-induced suppression of melatonin secretion. mRGCs also seem to be implicated in behavioural responses such as mood (Hattar et al., 2006; Ksendzovsky et al., 2017) and in vision forming pathways via input from the classical photoreceptors, the cones and rods. Recently, the role in colour vision and brightness perception has been described (Schmidt et al., 2014; Spitschan et al., 2017; Cao et al., 2018; Woelders et al., 2018; Zele et al., 2018).

Since the discovery in melanophores of frog skin (giving it its name) (Provencio et al., 1998), melanopsin was found in a subset of RGCs in mouse and monkey (Provencio et al., 2000), and was elegantly demonstrated in a later study to render these cells intrinsically photosensitive (Berson et al., 2002). Subsequently, melanopsin cells were detected in the human retina (Hannibal et al., 2004; Dacey et al., 2005). The discovery of the melanopsin system in the mammalian retina and its important role in NIF functions explains the fact that blind people with loss of vision due to diseases in the outer retina maintain the ability to stay photoentrained and have an intact pupillary light reflex.

Diseases involving the neuroretina may affect mRGCs or input pathways and for this reason symptoms representing NIF behaviour and physiology should be routinely investigated during elucidation of eye diseases.

In the present review, we will evaluate the implication of melanopsin RGCs in human diseases after a short description of the melanopsin system in humans.

2. Melanopsin-expressing RGCs in the human retina

Melanopsin-expressing RGCs in the human and primate retina have many similarities with mRGCs in other mammalian species. Initially, two subtypes of cells were described in rodents, and were classified based on the localization of their soma either in the ganglion cell layer (GCL) or in the inner nuclear cell layer (INL), as well as by their content of melanopsin (Do and Yau, 2010). M1 cells were found in the GCL and in the INL and have a high content of melanopsin, while M2 cells were found in the GCL and have a significantly lower content of melanopsin (Hughes et al., 2012). In mouse, two different forms of OPN4 were identified, a long and a short isoform, while M1 and M3 cells express the short form, the long isoform is expressed in all the mRGCs (Pires et al., 2009). A similar classification was also used in the human and primate retina (Hannibal et al., 2004; Dacey et al., 2005). However, later studies in both rodents (Schmidt et al., 2011) and humans identified at least 5 subtypes of mRGCs, named M1-M5. Furthermore, M1 cells can be subclassified based on soma size, "gigantic M1 (GM1)", and the location of their cell bodies in the GCL or displaced in the INL (dM1) (Liao et al., 2016; Esquiva et al., 2017; Hannibal et al., 2017) (Fig.1).

The different subtypes of mRGCs are widely distributed in the entire retina and the total number of mRGCs varies from 0.2-0.8 % of the total number of RGCs. This is most likely due to the antibodies avidity and immunohistochemical amplification techniques used in the different studies. Although the amount of mRGCs subtypes and their distribution in the retina differs between studies, the highest content of mRGCs is found in the fovea and perifoveal retina and the lowest content in the peripheral retina (Fig. 2-3) (Dacey et al., 2005; Hannibal et al., 2004, 2017; Liao et al., 2016; Esquiva et al., 2017; Nasir-Ahmad et al., 2017). M1 cells constitute the majority of mRGCs, while M2 and M4 cells are found in higher density in the nasal retina (Fig. 2).

Human and primate melanopsin cell bodies have their dendritic stratification in the innermost stratum of the inner plexiform layer (IPL, S5) and in the outermost stratum (S1) (Hannibal et al., 2004, 2014; Dacey et al., 2005; Dkhissi-Benyahya et al., 2006; La Morgia et al., 2010; Neumann et al., 2011). One subtype classified as M3 presents their dendritic stratification in both S1 and S5 strata of the IPL (Fig. 1) (Liao et al., 2016; Esquiva et al., 2017; Hannibal et al., 2017).

The different subtypes and the uneven distribution of melanopsin cells in the human retina seem to be associated with different NIF functions, as the different expression levels of melanopsin immunoreactivity in the various subtypes result in differences in "intrinsic" photosensitivity of the M1-M5 cells (Hannibal, 2006; Pires et al., 2009; Berson et al., 2010; Ecker et al., 2010).

mRGCs also express "extrinsic" photosensitivity due to different inputs to the various subtypes (Fig.1). In primates, including human retina, inputs to the mRGCs have been demonstrated in both inner and outer retina projecting dendrites showing synaptic appositions (Liao et al., 2016) with bipolar cells expressing the synaptic ribbon marker Ctbp2 (Jusuf et al., 2007; Grünert et al., 2011a; Hannibal et al., 2017). The Ctpb2-containing synapses of bipolar cells have been suggested to mediate a yellow-ON response (Dacey et al., 2005). Specifically, rod bipolar axon terminals have been found in close apposition with M1, GM1, M2, and M4 cells in the GCL/innermost layer of the IPL (Hannibal et al., 2017). Furthermore, mRGCs also receive inputs from cone bipolar cells (Dacey et al., 2005; Grünert et al., 2011b; Liao et al., 2016). In addition, mRGCs receive input from different kinds of amacrine cells (Bordt et al., 2017). Of these, AII amacrine cells make synaptic appositions with the innermost ON layer of the IPL, mostly with M1 and GM1 cells, and dopaminergic and GABAergic processes from amacrine cells to the outermost OFF layer of the IPL (Hannibal et al., 2017; Nasir-Ahmad et al., 2017; Vugler et al., 2007)(Fig. 1).

The melanopsin-expressing RGCs constitute the neuronal monosynaptic pathway to retinal target areas in the brain involved primarily in non-image perception, a pathway known as the retino-hypothalamic tract (RHT) (Hannibal and Fahrenkrug, 2006). The major target areas of the RHT in primates are the brain clock located in the suprachiasmatic nucleus (SCN), the pretectum, the lateral geniculate complex (Hannibal et al., 2014), and the superior colliculus and the pretectum (Dacey et al., 2005; Hannibal et al., 2014). In primates, both the pretectum and the superior colliculus are involved in image forming perception (Dacey et al., 2005).

3. mRGCs in the aging human retina

During aging, many circadian regulated functions such as melatonin secretion, cortisol secretion and core body temperature are disrupted (Cajochen et al., 2006) with decreased amplitude, phase advancement and/or altered circadian period (Myers and Badia, 1995; Cajochen et al., 2006). Especially the sleep/wake cycle is often found affected in the elderly (Van Someren, 2000).

Several factors seem to be associated with circadian dysfunction in the aging process. While neurodegenerative changes in the SCN may alter the temporal organization of this structure, altered light perception caused by a reduction in the capacity to transmit short wavelength light due to a semicataractous lens is observed in aged people (Hofman and Swaab, 2006). In addition, aging affects retinal functions and produces many degenerative changes in the retina and optic nerve (Johnson et al., 1987; Gao and Hollyfield, 1992; Curcio and Drucker, 1993; Harman et al., 2000; Eliasieh et al., 2007). These include the loss of RGCs (La Morgia et al., 2016), which has been associated with the disturbances in circadian timing (Van Someren, 2000; Karasek and Reiter, 2002). Alterations in retinal functions include disturbances in electroretinographic responses (Jackson et al., 2002), contrast and visual field sensitivity (Johnson et al., 1989; Elliott et al., 1990; Spry and Johnson, 2001), and adaptation to darkness (Jackson et al., 1999). Although mRGCs have demonstrated a high resistance to injury even in advanced stages of retinal degeneration (Esquiva et al., 2013; Cuenca et al., 2014; García-Ayuso et al., 2015; Lax et al., 2016), recent studies showed that in humans the mRGCs density and plexus decrease with age, correlating with the circadian rhythm dysfunction observed in people over 70 years of age (La Morgia et al., 2010; Esquiva et al., 2017). These observations in the human retina correspond to observations that have also been described in rodents (Semo et al., 2003b). Furthermore, the presence of lipofuscin found in melanopsin cells of increasing age could influence their functionality (Vugler et al., 2007). Lipofuscin is an autofluorescent photoinducible free radical generator which accumulates with age in active cells (Sparrow and Boulton, 2005). This accumulation of lipofuscin in mRGCs may lead to disrupted function and may play a significant role in the alterations of circadian rhythms with aging in humans (Hofman and Swaab, 2006).

4. mRGCs in human diseases

4.1 Alzheimer

Alzheimer's disease (AD) is a chronic neurodegenerative disease and the most common cause of dementia in older adults, characterized by the accumulation of amyloid-β protein in both cerebral and retinal blood vessels and neurofibrillary tangles (Arriagada et al., 1992). The disease is characterized by memory loss and can include confusion and behavioural disorders.

In addition to circadian alterations of melatonin, temperature rhythms and rest-activity, disruptions have been described in AD (Tranah et al., 2011) correlating with the severity of dementia (Dai et al., 1998), although not progressing at the same rate (Hatfield et al., 2004). Circadian rhythm dysfunctions are frequent in aging, but are even more pronounced in AD (Wu and Swaab, 2007) and the neuronal loss in the SCN has been considered one of the major risk factors for the circadian rhythms disturbances (Swaab et al., 1985; Stopa et al., 1999;Harper et al., 2008).

However, the loss of RGCs and/or degeneration of axons in the optic nerve has also been reported in AD patients (Hinton et al., 1986). The optic nerve shows a predominant loss of the magnocellular RGCs known to mediate specific visual funcions (Sadun and Bassi, 1990). AD neuropathy also affects the inner retina (Blanks et al., 1989). Interestingly, the decrease in RGCs is greatest in the central zone, more specifically in the foveal and parafoveal zone of the retina (Blanks et al., 2012), confirmed by OCT studies showing a significantly reduced number of RGCs in AD retinas vs. controls in the macular zone (Cheung et al., 2015), which is the area with the highest number of mRGCs. Despite the loss of mRGCs observed with aging that may contribute to circadian dysfunction in AD alone, a recent study described a greater loss of mRGCs in AD patients in comparison with controls of the same age. In this study a total loss of RGCs was reported, but mRGCs were specifically affected in AD, degenerating before visual bearing RGCs, even in younger patients with a normal RGCs count (La Morgia et al., 2016). Moreover, AD deposits were found inside and around the remaining mRGCs, which showed morphological abnormalities with a reduction of the dendritic diameter and axonal loss. Thus, it was proposed that mRGCs are primarily affected by AD pathology and their loss

may contribute to the circadian dysfunction described in AD (La Morgia et al., 2016). Interestingly, this loss could be correlated with another NIF function of mRGCs, a reduction in amplitude of PLR (Tales et al., 2001; La Morgia et al., 2016).

4.2 Parkinson

Parkinson's disease (PD) is the second most common neurodegenerative disease, characterized by the loss of dopaminergic neurons in the *substancia nigra*, the formation of Lewy bodies, and the accumulation of α-synuclein phosphorylated at serine-129 (p-α-syn) (Fahn, 2006; Beach et al., 2009).

PD patients mainly suffer from motor clinical features such as rigidity, tremor, and bradykinesia (Fahn, 2006; Postuma et al., 2015; Ferreira and Massano, 2017). However, several non-motor symptoms including cognitive decline (Caballol et al., 2007), mood disturbance (Tan, 2012), visual disruption (Archibald et al., 2009; Weil et al., 2016), impairment of the pupillary reflex response (Wang et al., 2016), sleep dysregulation (Fahn, 2006; Postuma et al., 2015) and alteration of the circadian regulated secretion of melatonin also occur in PD (Bordet et al., 2003).

Visual problems include dry eyes, blinking, colour vision alterations, impaired motion perception, and lower contrast sensitivity (Archibald et al., 2011; Lin et al., 2015). The contrast sensitivity abnormalities are explained by the retinal dopaminergic depletion that occurs in PD (Bodis-Wollner, 1990; Harnois and Di Paolo, 1990). The connectivity between dopaminergic amacrine cells, RGCs and mRGCs (Zhang et al., 2008) could also explain the loss of RGCs occurring in PD (Lee et al., 2014; Yu et al., 2014) affecting above all the temporal sector of the optic nerve (La Morgia et al., 2013; J.G. Yu et al., 2014) containing the parvocellular component, in contrast to what has been described in AD above, which mainly affects magnocellular RGCs (La Morgia et al., 2017).

Dysfunction of circadian rhythms in PD has been explained recently among different mechanisms by the occurrence of Lewy pathology in the SCN from PD patients (De Pablo-Fernández et al., 2018). However, the occurrence of retinal pathology involving mRGCs may also contribute to circadian disturbance. Two studies have recently reported the presence of α-synuclein in the inner retina of PD patients in large cells

resembling mRGCs (Beach et al., 2014; Bodis-Wollner et al., 2014), and it was recently shown that mRGCs are lost in PD patients compared to control subjects and furthermore, the remaining mRGCs demonstrated morphological alterations (Ortuño-Lizarán et al., 2018). As retinal mRGCs are responsible for light entrainment of circadian rhythms and nocturnal melatonin secretion and are involved in mood and sleep regulation, these morphological alterations in mRGCs could explain the circadian disruptions found in PD patients.

4.3 Diabetic retinopathy (DR)

Diabetic retinopathy (DR) is characterised by alterations in the retinal vasculature and is one of the major complications of diabetes (Keats and Khan, 2012) and the major cause of preventable blindness in developed countries (Congdon, 2003). DR symptoms can include floaters (dark spots), blurred vision, impaired colour vision, and vision loss (Cheung et al., 2010). Non-proliferative diabetic retinopathy is characterized by a breakdown of the blood-barrier, mycroaneurysm, pericyte, and vascular smooth muscle cell dropout and haemorrhages. Furthermore, in the advanced stages of the disease, in the proliferative phase, there is angiogenesis which can even lead to retinal detachment (Fletcher et al., 2007a; Curtis et al., 2009). Despite its vascular nature, DR is also a neurodegenerative disease and clinical symptoms often occur after an alteration in the retina at the molecular, cellular and functional level (Bearse et al., 2004; Fletcher et al., 2007b; Ng et al., 2008; Ola and Alhomida, 2014), affecting all types of retinal cells (Barber et al., 1998; El-Asrar et al., 2004; Kern and Barber, 2008). In a recent study, the expression of mRGCs in the ganglion cell layer and the inner nuclear layer of the human retina was found to be significantly reduced compared to age comparable control group (Obara et al., 2017). This loss could explain the alteration in circadian rhythms and sleep disturbances found in patients with severe DR and may also explain the pupillary defects and the abnormal regulation of melatonin and blood pressure during the day (Hikichi et al., 2011; Afsar, 2015; Kadono et al., 2016).

Altered post-illumination pupil response (PIPR) seems to develop prior to neurodegeneration of conventional RGCs (Su et al., 2008; Feigl et al., 2012) and could be used to identify early neurodegeneration at the initial stages of DR (see also below).

4.4 Mitochondrial optic neuropathies

Optic neuropathies due to mitochondrial dysfunctions found in Leber hereditary optic neuropathy (LHON) and dominant optic atrophy (DOA) are characterized by the loss of RGCs leading to the loss of vision (Carelli et al., 2004). Despite blindness, patients with these diseases preserve the pupillary light reflex (Wakakura and Yokoe, 1995; Bremner et al., 2001; Kawasaki et al., 2010; Ba-ali and Lund-andersen, 2017), light-induced melatonin suppression (Czeisler et al., 1995; Hatonen and Santavuori, 1998; Pérez-Rico et al., 2009), and intact circadian rhythm regulation (Moura et al., 2013).

La Morgia et al corroborate the preservation of NIF functions carried out by mRGCs in these mitochondrial optic neuropathy patients and while mRGCs are lost and impaired in the elderly, they resist neurodegeneration due to mitochondrial dysfunction, while other RGCs are not resistant (La Morgia et al., 2010). These findings are in concordance with the preservation of the retinofugal pathway to the olivary nuclei of the pretectum described in LHON, the main target areas of mRGCs (Bose et al., 2005).

Several authors provide supporting evidence for the resistance of mRGCs to different injuries (Vugler et al., 2008; Cui et al., 2015). It has been suggested that factors contributing to the resistance of mRGCs, such as the abundant mitochondrial population found in these cells, result in specific metabolic properties and higher mitochondrial activity compared to the rest of RGCs (La Morgia et al., 2011). This could be coupled to their intrinsic photosensitivity provided by the melanopsin photopigment, which may protect from light damage and ROS overproduction (Osborne et al., 2014; González-Menéndez et al., 2015). Another possibility suggested is the expression of the neuroprotective pituitary adenylate cyclase-activating polypeptide (PACAP) in mRGCs (Hannibal et al., 2004) which could be involved in the increased resistance to injuries, although this is still being debated (Hannibal et al., 2002, 2004; Georg et al., 2017).

4.5 Glaucoma optic neuropathy

Glaucoma is an ocular neuropathy characterized by ganglion cell death and optic nerve fibre loss, resulting in a loss of peripheral vision (Weinreb et al., 2014). This loss of RGCs is more selective on magnocellular RGCs losing larger optic nerve fibres more rapidly and resembling the axonal loss described in AD (Quigley et al., 1988). The loss of RGCs is probably due to two common events in the pathophysiology of glaucoma, the increased intraocular pressure and the vascular dysregulation (Gupta et al., 2009).

In glaucoma patients, a number of symptoms related to loss of mRGCs functions has been described, such as the loss of circadian rhythms (Jean-Louis et al., 2008; de Zavalía et al., 2011), impairment of the pupillary light reflex (Feigl et al., 2011; Kankipati et al., 2011; Nissen et al., 2014; Obara et al., 2016), and an alteration of the PIPR (Feigl et al., 2011). Similar alterations have been found in an animal model of chronic ocular hypertension and glaucoma which demonstrates a reduced density of mRGCs (de Zavalía et al., 2011). However, studies of mRGCs in another animal model of glaucoma of high intraocular pressure obtained opposite results regarding mRGCs survival, indicating that several pathological mechanisms of glaucoma co-exist (Li et al., 2006).

However, the functional alterations of glaucoma have been corroborated more recently by *Obara et al*, who found a decrease in the density of mRGCs in human retinas with advanced stages of glaucoma, and with a significant loss primarily in the GCL and sparing of mRGCs in the INL (Obara et al., 2016). Moreover, a decreased PIPR in advanced glaucoma (Rukmini et al., 2015) seems to correlate with visual field defect (Kankipati et al., 2011), suggesting that advanced glaucoma affects both non-image forming (mRGCs) and image-forming function.

4.6 Retinitis pigmentosa

Retinitis pigmentosa (RP) is an inherited neurodegenerative retinal disease characterized by a progressive peripheral and night vision loss because of different mutations in the rhodopsin encoding gene leading to rod degeneration at early stages. This rod disturbance leads to cone impairments with a consequent central vision loss in advanced stages of the disease and the loss of photoreceptors is accompanied by

degenerative changes in the inner retina (Marc et al., 2003; Kolomiets et al., 2010) and a degeneration of RGCs (García-Ayuso et al., 2010).

P23H mutation in the rhodopsin gene is the most prevalent in RP patients (Dryja et al., 1990). Recently, NIF function such as circadian dysfunctions (Lax et al., 2011, 2016) and a significantly reduced PLR were demonstrated in patients with RP (Kardon et al., 2011). In accordance, RP patients have been shown to exhibit sleep/wake disorders (Gordo et al., 2001; Ionescu et al., 2001) and circadian rhythm alterations of blood pressure and heart rate (Cugini et al., 2001). In a casuistic report, patients with RP demonstrated a severe degeneration in all layers of the retina and only few mRGCs were identified (Hannibal et al., 2004). In a rat model of RP, the degeneration of mRGCs was relatively belated compared to non-melanopsin RGCs (Esquiva et al., 2013), corroborating previous studies in other animal models of RP (Semo et al., 2003a; Vugler et al., 2008). The decrease of mRGCs only in advanced stages of retinal degeneration supports the previous described resistance to cell injury (Robinson and Madison, 2004; Li et al., 2006, 2008).

4.7 Migraine (photophobia)

Migraine is a common episodic neurological dysfunction characterized by increased sensory perception (Noseda et al., 2010a). Migraine pain was thought to originate in different cortical areas, including the visual cortex, but recently it was suggested that the migraine process may occur at a retino-cortical pathway (Evans and Digre, 2003; Noseda and Burstein, 2011). This painful photophobia depends on both the optic and trigeminal nerve integrity (Lebensohn, 1951).

Migraineurs suffer from photophobia, experiencing headaches that intensify with light, increased perception of brightness, and visual discomfort. These alterations in the visual system give rise to visual hallucinations and visual aura (Noseda et al., 2018).

Much progress has been made in the knowledge of the visual pathways that contribute to photophobia in migraine, and recently activation of abnormal cone-driven retinal pathway has been proposed (Noseda et al., 2016) causing negative emotions during the migraine (Noseda et al., 2017).

Studies on photophobia in blind persons with intact inner retina/optic nerve and blind persons without optic nerve/eyes observed that blind subjects who still maintained light perception also presented photophobia in migraines, while blind subjects who no longer had any type of light perception did not present photophobia (Noseda et al., 2010b). These observations indicate a role of mRGCs in photophobia and migraine. Furthermore, mRGCs may control light aversion and negative phototaxis (Johnson et al., 2010; Matynia et al., 2012). However, future studies are needed to clarify neuronal pathways and mechanism coupling input from mRGCs and activation of the trigeminal nociceptors involved in painful photophobia (Dolgonos et al., 2011).

4.8 Seasonal affective disorder (SAD)

Seasonal affective disorder (SAD) is a subtype of mood disorder characterized by recurrent episodes of major depression occurring with a seasonal pattern starting during fall and winter and with full remission during spring and summer (Rosenthal et al., 1986). One major reason for the development of this condition seems to be the lack of bright light, supported by the efficacy of bright light therapy (Terman and Terman, 2005). With the discovery of mRGCs it has been hypothesized that light transmitted via the RHT regulating non-image forming functions, including melatonin secretion, could be involved in SAD (McClung, 2007). Melatonin is a night signal released from the pineal gland and targets the brain clock located in the SCN. Melatonin is strongly regulated by the SCN and by light, and the circadian secretion of melatonin is delayed in SAD patients compared to normal controls (Lewy et al., 1998; Pandi-Perumal et al., 2007). Bright light in the morning seems most effective due to its phase shifting properties causing early morning phase advance of the clock (Lewy et al., 1987), leading to synchronization of the circadian rhythm of melatonin and the sleep/wake cycle (Pandi-Perumal et al., 2007).

Demonstration of a missense variant (P10L and 1394T) of the melanopsin gene (OPN4) which may affect NIF light transmission has been associated with the occurrence of SAD (Roecklein et al., 2013, 2009). Furthermore, the PIPR often used for the evaluation of mRGCs function (see below) demonstrated that the 1394T, but not the P10L genotype,

was affected in SAD patients (Roecklein et al., 2013). Interestingly, a study in non-seasonal major depression found normal PIPR in depressed patients similar to controls, suggesting that melanopsin function plays a minor role in the development of major depression (Feigl et al., 2018) .

5. Functional evaluation of the non-image forming system

Since the discovery of the melanopsin system in the mammalian eye, functional methods for evaluation of the NIF system is needed. Melanopsin-expressing RGCs located in the inner retina demonstrate a high sensitivity for blue light with a higher threshold of activation compared to the rods and cones located in the outer retina. Both rods and cones contribute in the input to the mRGCs during non-image forming light perceptions (Do and Yau, 2010; Liao et al., 2016; Hannibal et al., 2017; Nasir-Ahmad et al., 2017). A simple, non-invasive method that seems to be able to discriminate diseases affecting the inner and outer retina is to measure the pupillary light responses (PLR) (Nissen et al., 2015; La Morgia et al., 2018; Rukmini et al., 2019) . PLR are dependent on the integrity of mRGCs projections and the interaction between the outer and inner retinal photoreception, thereby indicating both outer retinal function of rod and cone photoreceptors, and inner retinal functions from mRGCs (Spitschan and Woelders, 2018; Kelbsch et al., 2019) .

In fact, PIPR and chromatic pupillometry may become clinical indicators of progressive changes in the retina (Ostrin et al., 2018) and a tool to evaluate the integrity of visual functions and localize retinal dysfunctions in various ocular diseases, like glaucoma and diabetes.

6. Conclusions

While it is well established that the loss of mRGCs is involved in circadian rhythms, sleep, cognitive, and mood pathologies, the role of these cells in different disorders is beginning to be understood. Recent research is stating the functions of mRGCs in human

visual and non-visual diseases with advances in the description of the activity of these cells with aging, and in different diseases.

The discovery of the melanopsin system in the mammalian eye highlights the importance of the regulation of non-image forming function, which can be present even in cases of severe blindness. The measurement of PLR, which is already being used in some diseases such as age-related macular degeneration or diabetic retinopathy, may provide information on the state of the mRGCs and seems to be a promising technique for clinical evaluation in the control and progression of diseases involving the inner (mRGCs) and outer retina.

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Figure legends

Fig. 1

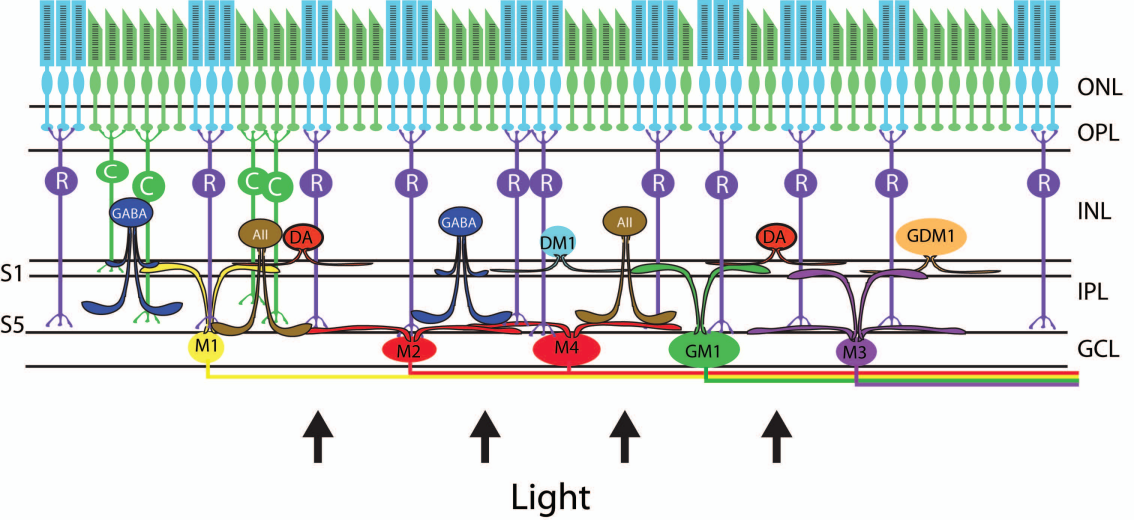
Schematic vertical section of the human retina showing rods and cones (blue and green) and the diverse subtypes of melanopsin expressing retinal ganglion cells (mRGCs). Human mRGCs were sub-classified as M1, displaced M1 (DM1), M2, M3, and M4 cells. Furthermore, gigantic M1 cells located in the ganglion cell layer (GCL) (GM1) and displaced in the inner nuclear cell layer (INL) (GDM1) are shown. Dendritic processes from M1, GM1, GDM1and DM1 and M3 cells terminates in S1 of the inner plexiform layer (IPL) and dendritic processes from M2, M4 and M3 cells terminates in S5. Synaptic apposition between mRGCs and amacrine cells are found in S1, while synaptic appositions between mRGCs and rod bipolar cells are found in S5. ONL; outer nuclear cell layer, OPL; outer plexiform layer. (reproduction with permission from Wiley Global Permissions, reproduced from: *J Comp Neurol*, **525**, 1934-1961, 2017.

Fig.2

Melanopsin immunoreactive retinal ganglion cells in a female human retina (age 67) with a total of 7046 mRGCs. M2 and M4 subtype of mRGCs are shown in red dots, other subtypes (see Fig. 1) are marked by green dots. Note the higher density of M2/M4 cells in the nasal part of the retina.

Fig. 3

Melanopsin immunoreactive RGCs in the human retina representing an area with high cell density (A) of the perifoveal/foveal retina and with low density of cells (B) from the peripheral retina.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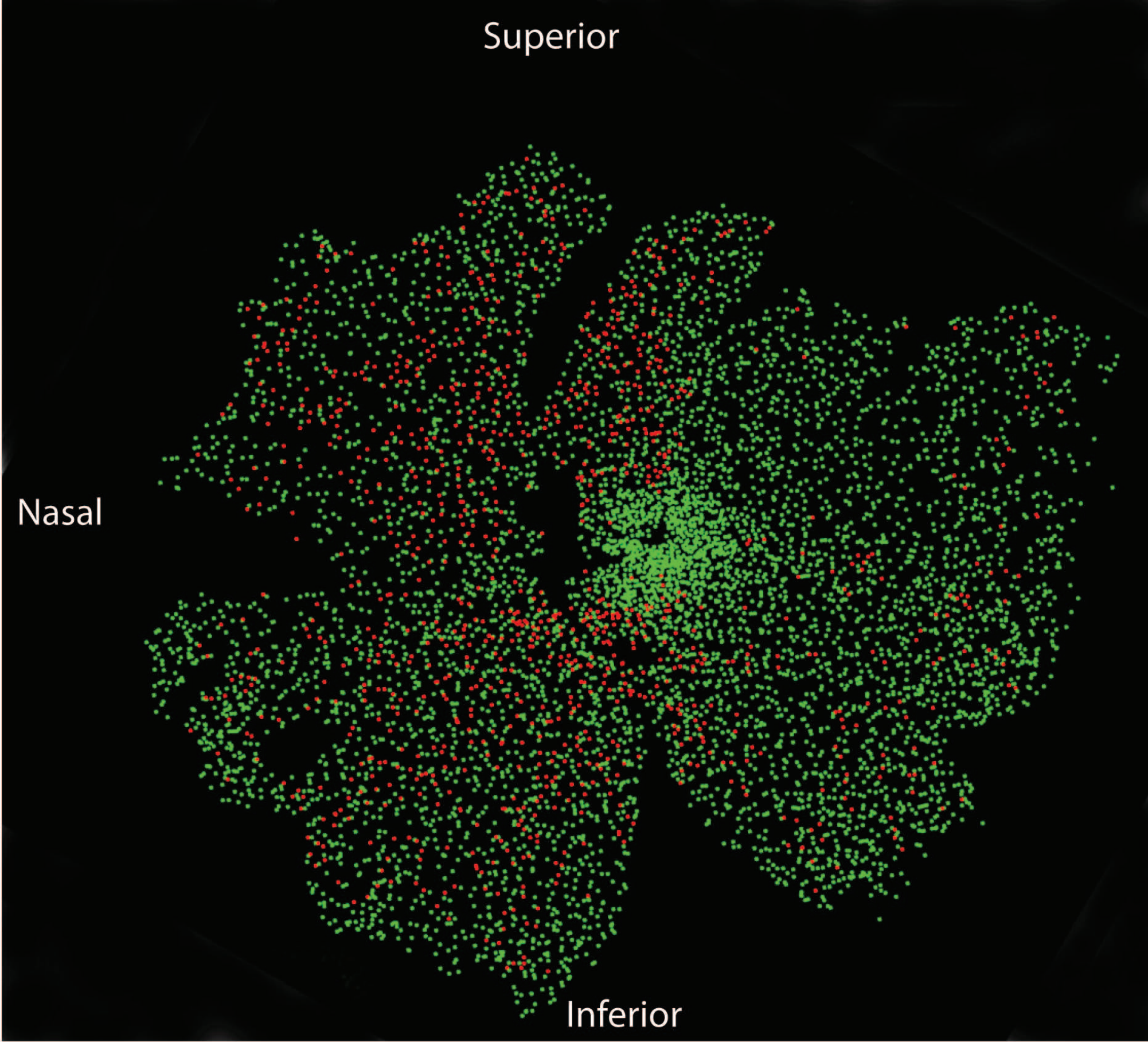
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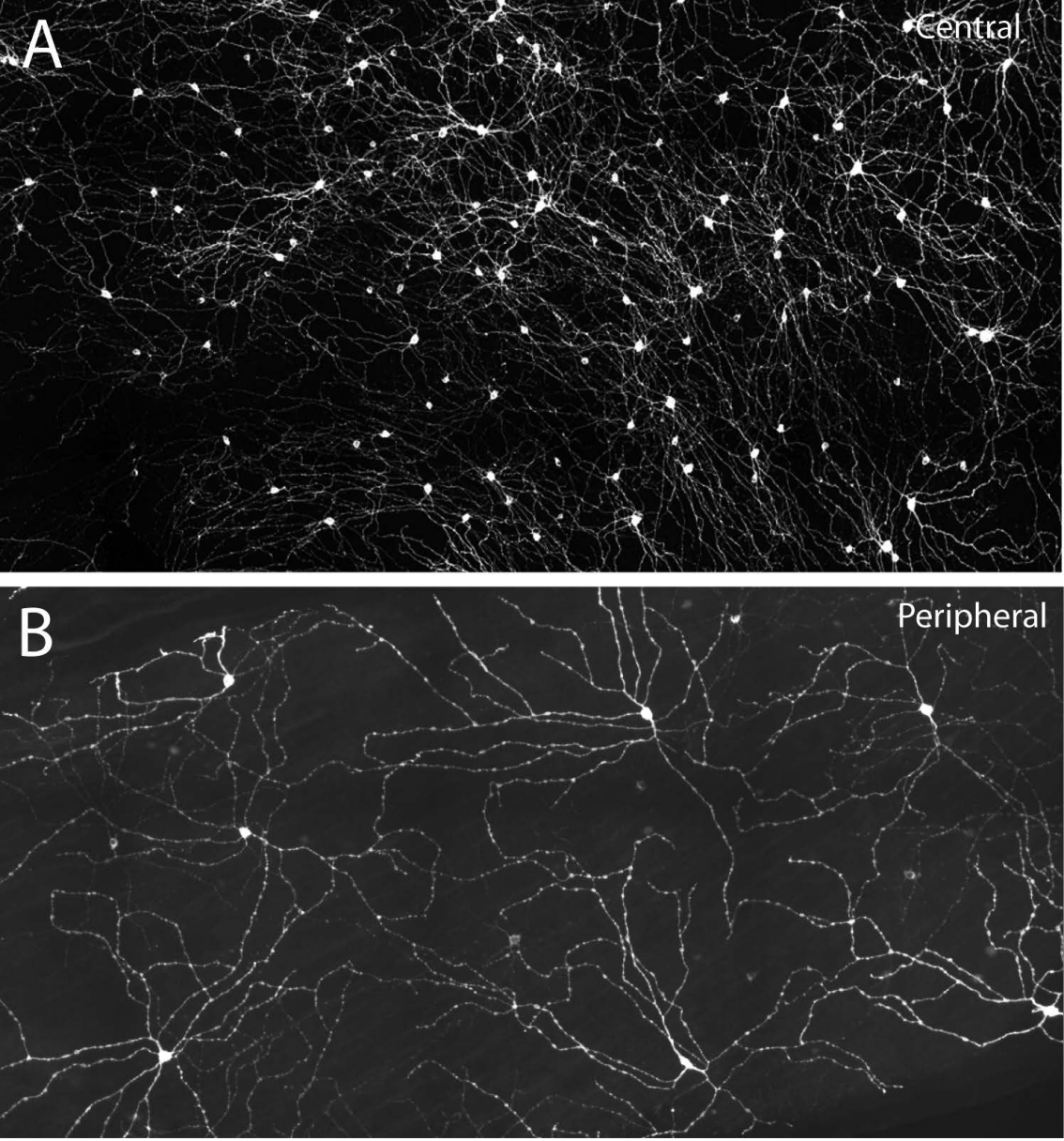
A
Central
B
Peripheral